Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1 and 19 are amended, claims 4 and 55-57 are canceled herein, and claim 59 is added. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which are present in a continuation of the present application. Claims 1-3, 8-11, 19-21, 23-37, 41-43, 46-54, and 58-59 are now pending in this application.

The Examiner is respectfully requested to rejoin claims 49-54 with the elected claims, i.e., claims 1, 4-7, 9-11, 19-20, 23, and 46-47, once the elected claims are found to be allowable.

Claim 57 is canceled specifically to delete the presence of two identical claims numbered 57. The subject matter of canceled claim 57 appears in new claim 59.

Support for new claim 59 is found at page 91, lines 9-18 and in Figures 19 and 25 of the specification.

At pages 3, 5, 6 and 7 of the Office Action, the Examiner states that the previous § 102 and obviousness-type double patenting rejections of claims 4, 10 and 11 are withdrawn in view of Applicant's amendments to the claims which indicate that the *cis*-acting transcriptional regulatory elements are not promoters and so are directed to claims that read on enhancers which are grouped with claims in Group III.

The Examiner is respectfully reminded that the pending independent claims include subject matter of the elected invention (e.g., see claims 9 and 20; one AAV vector has a heterologous transcriptional regulatory element which is a promoter that transcriptionally regulates an open reading frame in a second rAAV vector) and one of the nonelected inventions (e.g., claims 8 and 21; one AAV vector has a heterologous transcriptional regulatory element which is an enhancer that transcriptionally regulates an open reading frame in a second rAAV vector). Moreover, claims including claims 4, 10 and 11 were considered directed to the elected invention as of the Office Action dated March 11, 2003. Note that claim 4 is canceled solely due to the recitation in claim 1 that the second vector comprises the open reading frame.

The Examiner is requested to consider that pending claims 10 and 11 are drawn to the elected invention, e.g., claim 10 is directed to a first rAAV vector which includes a heterologous

transcriptional regulatory element, e.g., a promoter, which transcriptionally regulates an open reading frame in a second rAAV vector that does not include a heterologous promoter, and claim 11 is directed to a first rAAV vector which includes a heterologous promoter which transcriptionally regulates an open reading frame in a second rAAV vector that does not include a heterologous promoter. Accordingly, the Examiner is requested to reinstate claims 10-11 as claims currently under prosecution as those claims, contrary to the Examiner's assertion in the Office Action, read on the elected invention, i.e., an AAV vector which includes a heterologous *cis*-acting transcriptional regulatory element which is a promoter capable of regulating transcriptional expression of a therapeutic gene product encoded by another AAV vector.

Interview Summary

The Examiner is thanked for the courtesies extended to Applicant's Representatives in the telephonic interview conducted on September 2, 2004. In the Interview, Applicant's Representatives pointed out that the invention included rAAVs in which an open reading frame in one AAV vector is transcriptionally regulated by a *cis*-acting transcriptional regulatory element, e.g., a promoter and/or enhancer, in another AAV vector. It was also pointed out that the AAV vector with the open reading frame includes an ITR which may have promoter activity, i.e., a promoter may be present in the vector with the open reading frame (see claim 10 which is dependent on claim 1), although the transcriptional expression of that open reading frame is regulated by a *cis*-acting regulatory element provided by a different rAAV vector. However, in the Interview Summary dated September 7, 2004, the Examiner characterized the discussion of how the references differ as "[t]he cis-regulatory element of the first AAV regulates the transcription of the open reading frame in the second AAV and that the second vector does not have a heterologous promoter". While this reflects one embodiment of the invention (claim 10), it does not reflect the scope of the elected invention, e.g., see claim 9, discussed during the interview.

The 35 U.S.C. § 112 Rejection

Claims 57 and 58 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

Applicant discloses the use of AAV vectors for *cis*-activation (page 10, lines 9-20 and Figures 20-21), i.e., a large regulatory element(s) in a rAAV vector that is introduced into cells by one rAAV, can regulate in *cis* expression of a transgene delivered by another rAAV, which is in contrast to the use of two splicing vectors (page 91, lines 9-18 and Figures 19 and 25).

Thus, withdrawal of the § 112(1) rejection is respectfully requested.

The 35 U.S.C. § 102 Rejections

The Examiner rejected claims 1, 9, 46-47, and 55-56 under 35 U.S.C. § 102(e) as being anticipated by Engelhardt et al. (U.S. Patent No. 6,436,392). The Examiner also rejected claims 1, 9, 46-47, and 55-56 under 35 U.S.C. § 102(e) as being anticipated by Couto et al. (U.S. Patent No. 6,200,560) or Couto et al. (U.S. Patent No. 6,221,349). The Examiner further rejected claims 1, 9, 19-20, 46-47, 55-56, and 58 under 35 U.S.C. § 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology, 16:757 (1998)). These rejections are respectfully traversed.

It is disclosed in the '392 patent that recombinant adeno-associated virus (rAAV) vectors, each containing a promoter and an open reading frame between ITRs, may become linked after infection of the host cell with the vectors and synthesis of double-stranded viral DNA (column 4, lines 41-56 and column 5, lines 26-38). Other vectors disclosed in the '392 patent include rAAV vectors that contain an open reading frame flanked by a splice site, i.e., one rAAV vector contains a splice acceptor site and another rAAV vector contains a splice donor site, which vectors together encode a functional gene product (column 4, lines 57-column 5, line 25). It is disclosed that transcription of a molecule formed by linking the two rAAVs in a cell results in a spliced RNA molecule which encodes a functional peptide (column 49, lines 14-22).

In neither embodiment disclosed in Engelhardt et al. does the heterologous promoter in one rAAV vector regulate transcriptional expression of the gene product encoded by the other rAAV vector. Thus, Engelhardt et al. do not teach Applicant's invention.

The '560 patent issued from an application which is a continuation-in-part of the application which issued as the '349 patent. The '560 and '349 patents teach the use of rAAV vectors encoding Factor VIII, e.g., a Factor VIII which lacks the B domain (see Figures 1-3) or a fragment encoding the heavy or light chain of Factor VIII which may not be biologically active until administered to a subject that can supply the other chain (column 20, lines 1-19 of the '349 patent and column 20, lines 13-31 of the '560 patent). Example 1 of the '560 and '349 patents discloses two AAV vectors, each of which delivers different portions of the Factor VIII gene (one with the heavy chain coding region and the other with the light chain coding region) to cells. Both vectors employ the EF1α promoter and intron to express the heavy chain of Factor VIII or the light chain of Factor VIII (Figure 7).

As the '560 and '349 patents disclose two vectors each with its own promoter linked to an open reading frame for a chain of Factor VIII which can reassemble to form a biologically active Factor VIII, the '560 and '349 patents do not disclose Applicant's invention.

The Rendahl et al. article discloses two rAAV vectors, one having a tetracycline sensitive operator sequence linked to a minimal CMV promoter which controls expression of a murine erythropoietin (epo) transgene, and the other having a CMV promoter controlling expression of a tetracycline responsive transactivator, tTA (abstract and Figure 1), i.e., it is an operon like system. The two rAAVs were coinjected directly into the skeletal muscle of adult immunocompetent mice (abstract). It is disclosed that transcription of the murine erythropoietin transgene was controlled by systemic administration or withdrawal of tetracycline over an 18 week period, demonstrating that the two vectors were capable of transducing the same cell (abstract). Note that the CMV promoter in the vector encoding tTA does not regulate transcriptional expression of murine epo.

Accordingly, Applicant's invention is not disclosed in Rendahl et al.

Therefore, withdrawal of the § 102 rejections is respectfully requested.

The Obviousness-Type Double Patenting Rejection

The Examiner rejected claims 1, 9, 46-47, and 55-56 under the judicially created doctrine of obviousness-type double patenting over claims 8-15 of U.S. Patent No. 6,436,392. This rejection is respectfully traversed.

Claim 8 of the '392 patent is directed to a method to express a polypeptide in a host cell. The method comprises contacting a host cell comprising a first AAV vector comprising linked: i) a first DNA segment comprising a 5'-inverted terminal repeat (ITR) of AAV; ii) a second DNA segment comprising a splice acceptor site; iii) a third DNA segment comprising a portion of an open reading frame for a polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; with a second AAV vector comprising linked: i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a splice donor site; iii) a third DNA segment comprising a portion of an open reading frame which together with the DNA segment of (a)(iii) encodes a functional polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV so as to yield a host cell which expresses the functional polypeptide.

Claim 9 of the '392 patent is directed to a method to express a polypeptide in a host cell, comprising: contacting a host cell with a first AAV vector comprising linked: a) i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a portion of an open reading frame operably linked to a promoter; iii) a third DNA segment comprising a splice donor site; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; and a second AAV vector comprising linked: b) i) a first DNA segment comprising a 5'-ITR of AAV; ii) a second DNA segment comprising a splice acceptor site; iii) a third DNA segment comprising a portion of an open reading frame which together with the DNA segment of a) ii) encodes a functional polypeptide; and iv) a fourth DNA segment comprising a 3'-ITR of AAV; so as to yield a host cell which expresses the functional polypeptide. Claims 10-15 are dependent, in part, on claims 8-9.

Claims 8-15 of the '392 patent do not disclose or suggest a composition comprising at least two rAAVs, wherein one of the rAAVs comprises an open reading frame and the other rAAV comprises at least one *cis*-acting heterologous transcriptional regulatory element, wherein the *cis*-acting heterologous transcriptional regulatory element regulates transcriptional expression

of the therapeutic gene product encoded by the open reading frame after the host cell is contacted with the two vectors.

Hence, withdrawal of the obviousness-type double patenting rejection is appropriate and respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop RCE, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 19 day of October, 2004.

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